REMARKS

This document is responsive to the final Office Action mailed January 6, 2011, and is presented in lieu of an appeal brief with a Request for Continued Examination. The Notice of Appeal was received by the Office July 11, 2011. This document is being filed Monday, February 13, 2012; as such, the present document is timely filed.

Claims 1 and 4–29 were pending. Claims 4–7, 10–12, 16, and 24–29 have been withdrawn by the Examiner as being drawn to a non-elected invention, and Claims 1, 8, 9, 13–15, and 17–23 have been acted upon in this official action. The text of canceled Claim 3 has been removed from the claims section above to correct the claims in applicants' prior response. Claim 8 has been amended to depend from Claim 1 and not from canceled Claim 3. No new matter has been added by this amendment. Applicants respectfully request reconsideration of the claims in view of the above amendments and the following remarks. The rejoining of Claims 4–8, 10–12, 16, and 25–29 for prosecution of the entire invention as envisioned by applicants is also respectfully requested.

Applicants note that the prior rejection under 35 U.S.C. § 102 has been withdrawn.

Rejections Under 35 U.S.C. § 112

Claims 1, 8, 9, 13–15, and 17–23 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Office has alleged that the specification provides insufficient guidance to differentiate immature dendritic cells having CD1a and decreased CD14, from non-activated monocytic precursors, as broadly claimed. The Office has alleged that the instant claims are drawn to a method of differentiating monocytic precursors into immature dendritic cells having decreased expression of CD14 and increased expression of CD1a comprising contacting non-activated monocytic precursors with GM-CSF in the absence of additional cytokines. Further, the Office has characterized the state of the art as

being such that obtaining immature dendritic cells with GM-CSF in the absence of additional cytokines is extremely unpredictable. For example, the Office has cited Chaperot *et al.* as teaching a method identical to that of the instant claims, including culturing the monocyte precursors in non-adherent bags, but failing to obtain $CDla^+$ immature dendritic cells after culture in GM-CSF in the absence of additional cytokines. In addition, the Office has alleged that Chaperot *et al.* teach isolating the monocytic precursors by various methods including cytapheresis, density gradient preparation, and negative selection, which are conditions disclosed by the instant specification as "non-activating". Likewise, the Office has cited Bernard *et al.* for allegedly teaching a method identical to that of the instant claims, including culturing in PFTE bags, but again failing to obtain immature dendritic cells with reduced CD14 expression by culture with GM-CSF in the absence of additional cytokines.

Furthermore, the Office alleges that Sallusto *et al.* teaches the culture monocytic precursors in the presence of a medium containing 10% serum along with GM-CSF alone, which as disclosed by the instant specification prevents tight adherence and activation of the cells. However, the Office asserts that Sallusto *et al.* fail to obtain $CDla^+$ immature dendritic cells. Still further, the Office has cited other references (such as, Matera *et al.* and Kasinrerk *et al.*) for teaching methods that do obtain a population of $CDla^+$ cells displaying decreased expression of CD14 by culture in GM-CSF in the absence of additional cytokines. As such, the Office has alleged that it is not readily apparent which factors are critical for successfully obtaining said cells compared to the methods of Sallusto *et al.*, Bernard *et al.*, or Chaperot *et al.* Thus, the Office has determined that the art is of an extremely unpredictable nature and therefore, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims.

The Office has asserted that the instant specification teaches that the critical factor in obtaining immature dendritic cells by culture with GM-CSF in the absence of additionally cytokines relates to the activation status of the monocytic precursors. Further, the Office has asserted that the specification teaches that the monocytic precursors should be isolated and cultured in such a way as to prevent their activation. For example, the Office alleges that the instant specification discloses that non-activated precursors can be obtained by inhibiting the tight adhesion of monocytic precursors to the culture surface and that this inhibition of tight adhesion can be accomplished by a using low avidity culture vessels, or by including a high concentration of animal serum in the culture. Still further, the Office alleges that the instant specification discloses various methods for isolating the monocytic precursors such that they are non-activated, but the Office has alleged that the disclosed methods are the same as those taught in the prior art, including aphaeresis, centrifugation, or positive/negative selection.

In addition, the Office alleges that the instant specification further provides specific examples in which monocytic precursors are cultured with GM-CSF in the absence of additional cytokines to obtain $CDla^+$ immature dendritic cells. The examples are summarized by the Office as disclosing the culture of the cells in low-avidity bags, or with a high concentration of serum protein. However, the Office has cited both Bernard *et al.* and Chaperot *et al.* as having performed the method using a low avidity culture vessel and isolating the cells using a non-activating method, but having failed to obtain $CDla^+$ immature dendritic cells with reduced CD14 expression. Moreover, the Office has cited Sallusto *et al.* as having cultured monocytic precursors with 10% serum, which the Office has alleged the instant specification teaches as preventing tight adherence (and hence activation) of the precursors. However, the Office alleges that Sallusto *et al.* also failed to obtain immature dendritic cells after culture in GM-CSF alone. As such, the Office has alleged that it must be assumed that other critical factors are required to

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successfully perform the method of the instant claims, either in the cell isolation protocol or the cell culture conditions. Therefore, based on the unpredictability of the art, the Office has alleged that the instant specification does not provide sufficient guidance to enable one of skill in the art to obtain "non-activated" precursor as broadly claimed, that would result in a $CD1a^+$ immature dendritic cell after culture with GM-CSF in the absence of additional cytokines.

Applicants' arguments filed August 11, 2010, have been fully considered by the Office, but were not persuasive. In particular, the Office has summarized applicants' prior remarks as arguing that none of the cited references teach the same method as recited in the instant claims, and that the methods of Bernard *et al.* and Chaperot *et al.* must either begin with activated monocytic precursors, or the monocytes adhered to the bags during culture. Applicants' prior remarks were noted by the Office as stating that the skilled artisan would be able to alter the methods of Bernard *et al.* and Chaperot *et al.* using the teachings of the instant specification to obtain immature dendritic cells.

As above, the Office has alleged that Bernard *et al.* and Chaperot *et al.* teach isolating monocytes by aphersis/cytapheresis and/or density centrifugation. The specification at pages 6–7 is cited by the Office as specifically disclosing that non-activated precursor cells can be isolated by aphaeresis and differential centrifugation, exactly as performed by Bernard *et al.* and Chaperot *et al.* Furthermore, the Office alleges that Bernard *et al.* and Chaperot *et al.* teach culturing the precursors in hydrophobic PFTE bags, exactly as required by Claims 8–9. In addition, the Office alleges that Bernard *et al.* and Chaperot *et al.* specifically disclose the culture is an adherent free culture (see page 1672 of Chaperot *et al.* and page 17 of Bernard *et al.*). Thus, the Office concludes that the references teach the exact method of the instant claims, but fail to obtain dendritic cells having no expression of CD14 and increased expression of CDla. As such, the Office alleges that applicants have not identified any specific teaching in the instant

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specification that that can be used to modify the method of Bernard *et al.* or Chaperot *et al.* to obtain immature dendritic cells. Furthermore, the Office has noted that even if the specification does disclose such a teaching, that teaching is not part of the instant claims and therefore the claims do not recite any method steps that differentiate them from the method of Bernard *et al.* and Chaperot *et al.* Therefore, the Office has concluded that the claims are clearly missing essential steps that would enable the skilled artisan to obtain immature dendritic cells.

Still further, the Office has noted that in the prior response applicants further argue that it is known from the specification that some PFTE bags can activate monocytic precursors, and that, for example, high concentrations of an animal protein are required to prevent the activation of the precursor, as shown in Example 1. Chaperot *et al.* teach culturing the monocytes in culture medium comprising autologous plasma, which comprises high concentration of animal proteins. Thus, the Office has alleged that using animal protein does not appear to be a factor that enables production of immature dendritic cells. Regardless, it is noted that the instant claims do not require the presence of animal proteins to prevent activation/adhesion, and in fact, the claims specifically recite that adhesion/activation of the monocytes is inhibited by culture in a PFTE (*i.e.*, Teflon) bag, exactly as performed in the cited references. Moreover, Claim 13 specifically requires that the culture medium be serum free (*i.e.*, encompassing culture in the absence of animal serum proteins). Thus, neither the specification nor the claims define any method steps or elements that differentiate the claimed method from that taught by Chaperot *et al.* and Bernard *et al.* and that would enable the skilled artisan to produce immature dendritic cells.

Applicants again must respectfully disagree with the above rejection. Neither Chaperot *et al.* nor Bernard *et al.*, when considered alone or together, disclose the same method as described in the instant application. Chaperot *et al.* teach a method for obtaining macrophage

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and a method for obtaining dendritic cells. The methods use "non-adherent bags" with medium already used for therapeutic application. (See page 1672, right column, lines 3 and 4 from the bottom). There is no evidence provided in Chaperot *et al.* that the monocytes do not interact with the "non-adherent bag" to induce the differentiation of macrophage when the monocytes are cultured in the presence of GM-CSF alone. Applicants teach at paragraphs [0015] and [0016] that low avidity culture vessels, such as, Teflon® cell culture bags, can be used to decrease the adherence, and therefore activation, as monocytes during differentiation. Paragraphs [0069] and [0070], for example, disclose that high concentrations of animal or human protein (e.g., about 1% to about 10%) can be used to further decrease adhesion, in even Teflon® cell culture bags. Still further, Examples 4 through 6 demonstrate that the use of GM-CSF without other cytokines in combination with high concentrations of human serum albumin in a method culturing monocytes in Teflon® cell culture bags results in the production of immature dendritic cells and not macrophage. As such, the present specification provides sufficient guidance for the skilled artisan to modify the methods of Chaperot *et al.* to culture non-activated monocytes in a low avidity culture vessel with a culture medium supplemented with GM-CSF and no other cytokine to produce immature dendritic cells having no expression of CD14 and having increased expression of CD1a on the cell surface.

Contrary to the allegation of the Office, Chaperot *et al.* do not disclose a method using a high concentration of animal protein. In fact, Chaperot *et al.* disclose a method that results in the production of macrophage from monocytes that uses IMDM supplemented with 2% autologous plasma and GM-CSF. Human plasma is well known to the skilled artisan to contain about 7% protein. As such, as defined in the instant specification, Chaperot *et al.* would not be considered to use a high concentration of animal or human protein and, as previously stated by applicants,

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the skilled artisan would be able to alter the method taught by Chaperot *et al.* and obtain immature dendritic cells instead of macrophage.

Bernard *et al.* uses a method known to the skilled artisan to result in the production of macrophage from monocytes cultured in Teflon® cell culture bags. Like, Chaperot *et al.*, Bernard *et al.* refer to their culture method as being "adherent-free," at least in regard to the culture of monocytes with GM-CSF and IL-13 to obtain dendritic cells as compared with the usual methods that use adherence to plastic to obtain monocytes. Also like Chaperot *et al.*, Bernard *et al.* use a "low concentration" (as defined in the instant specification) of animal protein in the culture method. In particular, 5% fetal calf serum is used in the method for the induction of DC from monocytes. See page 19, left column, line 14. In the method to obtain macrophage, 5% human pooled AB serum was used. Both concentrations are well below the concentration of animal or human protein defined in the present specification as being desired to inhibit the formation of macrophage from activated monocytes cultured in medium supplemented with GM-CSF without any additional cytokines. As such, the specification as filed provides the skilled artisan with sufficient guidance to use the methods described by applicants to induce the differentiation of immature dendritic cells having no expression of CD14 and having increased expression of CD1a on the cell surface by culturing non-activated monocytic dendritic cell precursors in a cell culture medium supplemented with GM-CSF and without any additional cytokines. A method for differentiating human monocytic dendritic cell precursors into immature dendritic cells having CD1a on the cell surface, comprising: a) providing a cell population comprising non-activated human monocytic dendritic cell precursors; and b) contacting the non-activated monocytic dendritic cell precursors in a culture vessel with a dendritic cell culture media supplemented with granulocyte-macrophage colony stimulating factor in the absence of additional cytokines under conditions that prevent adhesion of the

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non-activated human monocytic dendritic cell precursors to the surface of the culture vessel and which do not activate the monocytic dendritic cell precursors for a time period sufficient for the human monocytic dendritic cell precursors to differentiate into immature dendritic cells having no expression of CD14 and having increased expression of CD1a on the cell surface has been described fully in the specification as required under 35 U.S.C. § 112, first paragraph. In view of the above remarks, applicants respectfully request the Office reconsider and withdraw the rejection of Claims 1, 8, 9, 13-15, and 17-23.

CONCLUSION

In view of the foregoing, applicants believe all issued raised by the Examiner have been addressed, and the claims now pending in this application are believed to be in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-695-1786.

Respectfully submitted,

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